ANIMAL HEALTH INSTITUTE

Representing manufacturers of animal health products

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Docket Management Branch (HFA 305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Approval of Subtherapeutic Uses in Livestock
Docket No. 99P 0485

These comments are submitted by the Animal Health Institute ("AHI") in response to the petition submitted by the Center for Science in the Public Interest and allied groups ("CSPI") requesting that FDA ban the subtherapeutic use in livestock of those antibiotics that may be used in, or are related to those used in, human medicine. Specifically, the CSPI seeks a ban on the subtherapeutic uses of penicillin, tetracyclines, erythromycin, lincomycin, tylosin, virginiamycin and other antibiotics used in human medicine or related to those used in human medicine. AHI is a national trade association representing manufacturers of animal health products – pharmaceuticals, vaccines and feed additives used in modern food production and the medicines that keep pets healthy.

It is the position of AHI that the issues raised by CSPI have in fact been reviewed extensively by FDA, and except with respect to penicillin and tetracyclines, resolved favorably to drug sponsors. There is no new evidence since 1977 that has not been reviewed by FDA or, under FDA contract, by the NAS-NRC, that resolves the controverted scientific issues pending with respect to penicillin and tetracyclines. Accordingly, there is no legal or factual basis for any new FDA initiative with respect to these drugs.

In support of its petition, the CSPI asserts that since 1977, when FDA initiated but did not complete proceedings to ban the subtherapeutic uses of penicillin and tetracyclines in animal feed, new research demonstrates that the use of antibiotics in livestock feed contributes to antibiotic resistance among food borne and other pathogens. The petition further asserts that the resistant bacteria can then be transferred to humans. In fact, however, FDA, using the mechanism of 21 C.F.R. § 558.15 with respect to drugs then on the market, and the criteria in that section with respect to later NADA submissions, has determined for most of the drugs identified by CSPI that they do not increase salmonella shedding or select for *E. coli* resistance in the target animals.

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Thus, FDA has already determined that a number of antibiotics are safe and effective for subtherapeutic use in livestock feed either individually or in specific combinations and under specified conditions of use. For example, erythromycin is approved for growth promotion, increased weight gain and/or improved feed efficiency in, *inter alia*, chickens, turkeys and swine (21 C.F.R. § 558.248), lincomycin is approved for increased weight gain and improved feed efficiency in chickens (21 C.F.R. § 558.325), tylosin is approved for increased weight gain and improved feed efficiency in chickens and swine (21 C.F.R. § 558.625), bacitracin zinc is approved for growth promotion, increased weight gain, increased egg production and/or improved feed efficiency in chickens, turkeys, pheasants, quail, swine and cattle (21 C.F.R. § 558.78), and bacitracin methylene disalicylate is approved for increased weight gain, increased egg production and/or improved feed efficiency in chickens, turkeys, pheasants, quail and swine (21 C.F.R. § 558.76).

Many of these same drugs are approved for prevention and/or control of disease in food animals. *Id.* These uses are important to the health of livestock and poultry, and are based on the medically accepted proposition, common to both human and veterinary medicine, that disease prevention and control are preferable, from a public health standpoint, to waiting to treat a full-blown disease.

All of these antibiotics, as well as others, have met the requirements for submission of additional safety and efficacy data set forth in 21 C.F.R. § 558.15(a) and (b). Under that regulation, drug sponsors were required to submit to FDA data "which resolve conclusively the issues concerning [the antibiotics'] safety to man and animals and their effectiveness under specific criteria established by the Food and Drug Administration...." 21 C.F.R. § 558.15(a). These data were required to include the effect of the subtherapeutic use of the drugs on the *Salmonella* reservoir in treated animals as compared with untreated controls. 21 C.F.R. § 558.15(b)(2) and (3). In other words, all of the drugs named by CSPI in their petition (excluding penicillin and tetracyclines) have been approved by FDA as safe and effective for subtherapeutic use in livestock feed as a result of submissions under 21 C.F.R. § 558.15, or in accordance with the criteria in that section[1]. Virginiamycin has been approved for increased weight gain and improved feed efficiency in chickens, swine and cattle (21 C.F.R. § 558.635), but is not listed in 21 C.F.R. § 558.15 as it was submitted for approval after the adoption of that regulation. However, virginiamycin was required to meet the same standards for salmonella shedding as all of the other drugs.

To revoke the approval of any antibiotics already approved for use in animal feed, FDA must follow the procedure set forth in 21 U.S.C. § 360b(e)(1), which states that after due notice and opportunity for hearing to the applicant, the Secretary shall issue an order withdrawing approval of a new animal drug application if the Secretary finds, *inter alia*,

[1] These drugs were subjected to these requirements regardless of whether the drug approvals were for prevention, treatment or control of disease, or for feed efficiency, increased weight gain or growth promotion.

(A) that experience or scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved ... [or]

(B) that new evidence not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the approved conditions of use.

Anyone seeking withdrawal of a drug approval must therefore demonstrate that experience; scientific data or new evidence shows that the drug is unsafe for use under the approved conditions of use for that drug. While this is a difficult standard to meet under any circumstances, it will be particularly burdensome in the case of drugs for which the information required by 21 C.F.R. § 558.15(a) or (b) has been submitted. In promulgating 21 C.F.R. § 558.15 and requiring drug sponsors to submit data on the effect of subtherapeutic use of the approved drug on the *Salmonella* reservoir in treated animals, FDA has already confronted and resolved the issue of safety of these drugs to man and animals. The standard of review of any new data in this area should therefore be especially rigorous.

In order to review the safety and effectiveness of these drugs, as CSPI requests, FDA must determine that new evidence raises an issue regarding whether each drug is unsafe for use under the approved conditions of use. Only then can FDA initiate the process of reviewing the approval of such drug pursuant to 21 C.F.R. § 12.1, *et seq.* CSPI's petition cites no such new evidence.

The CSPI petition correctly points out that Notices of Opportunity for Hearings were issued in the 1970s with respect to the subtherapeutic uses of penicillin, oxytetracycline and chlortetracycline, as well as for penicillin-streptomycin premixes. 42 Fed. Reg. 35220-21 (July 8, 1977); 43 Fed. Reg. 53827-28 (November 17, 1978); and 48 Fed. Reg. 4490-92 (February 1, 1983). Since the issuance of those notices, both FDA and the NAS-NRC have reexamined the controverted scientific issues in that proceeding, and neither has been able conclusively to resolve those issues in a manner that would lead to the holding of an evidentiary hearing. E.g., NRC, THE EFFECTS ON HUMAN HEALTH OF SUBTHERAPEUTIC USE OF ANTIMICROBIALS IN ANIMAL FEED (NAS, 1980). Although FDA can issue notices of hearing for these drugs, the agency would have to comply with all of the requirements associated with issuing such notices, including the assembly of all of the data, favorable and unfavorable, that the agency has in its files bearing on this safety issue with respect to these drugs. 21 C.F.R. §12.35 *et seq.* The CSPI petition provides no factual basis for the agency undertaking this effort.

In concordance with these regulatory and legal aspects of safety evaluations, three medical publications provide evidence that there is no human medical impact associated with growth promotion uses of antibiotics. Cherubin in 1981 stated that "the role of low-concentration, growth-promoting antibiotic feed supplements has been much discussed but never

has been delineated or proven. In fact, these supplements probably are totally irrelevant to the development of antibiotic resistance in salmonella." DuPont and Steele in 1987 concluded that "...it does not appear that the banning of drugs as feed additives, with concomitant unrestricted use of these agents for the treatment of both animals and people, would favorably influence the problems of antimicrobial resistance and salmonellosis in human populations." Lorian in 1986 evaluated antimicrobial susceptibility data on more than six million strains of bacteria to conclude that "Resistance to tetracycline in human strains has not increased in recent years; on the contrary it has decreased. Whatever role tetracycline has in animal feeds, it has not produced an effect in bacteria isolated from people." Also, in 1987, the FDA asked the Institute of Medicine to conduct an independent review of the human health consequences and the risk associated with the use of penicillin and tetracyclines at subtherapeutic concentrations in animal feed. The Committee reported a paucity of direct evidence implicating subtherapeutic use of antimicrobials as a potential human health hazard, and therefore primarily based its conclusions on indirect or circumstantial evidence. Estimates of excess mortality were extrapolated from their risk model, but were qualified as to their validity due to the quality of the database, assumptions, and other considerations.

CSPI points out that several antibiotic growth promoters have been removed from the market in Europe. In fact, the so-called "precautionary principle" has been invoked by the EU to suspend the growth promotion use of tylosin, spiramycin, virginiamycin, and bacitracin zinc; the therapeutic feed additive claims have been left in place for several of these products. This political decision by the EU commission has yet to be supported by scientific evidence. Indeed, the EU Scientific Committee for Animal Nutrition (SCAN) had previously reviewed the data on virginiamycin, tylosin, and spiramycin. In regard to tylosin and spiramycin SCAN concluded that "in the absence of sufficient research data on the epidemiology and spread of macrolide resistance, both among farm animals and from them to man, there is no reason for a general ban on the use of macrolides as feed additives." In a separate review of virginiamycin, "SCAN concludes that the use of virginiamycin as a growth promoter does not constitute an immediate risk to public health in Denmark." The Heidelberg Appeal Nederland Foundation reviewed approximately 275 papers to address the question as to what extent, if at all, the use of antimicrobial growth promoters in animal production contributes to bacterial antibiotic resistance in humans (Bezoen, 1999). Among their conclusions was that "so far, the use of antimicrobial growth promoters did not compromise the human therapeutic use of related antibiotics."

The CSPI cites the recommendations of the WHO consultation in Berlin (1997) which is stated as: "The recommendation made by the previous WHO advisory group (1994) is reinforced:

The use of any antimicrobial agent for growth promotion in animals should be terminated if it is:

- used in human therapeutics; or
- known to select for cross-resistance to antimicrobials used in human medicine."

This recommendation was made in tandem with the following statement: "Increased concerns regarding risks to public health resulting from the use of antimicrobial growth promoters indicate that it is essential to have a systematic approach towards replacing growth-promoting antimicrobials with safer non-antimicrobial alternatives." It was not the intent of the WHO to simply remove antimicrobial growth promoters without providing viable alternatives. Indeed, this concept is reinforced by the National Research Council which called for increased research on alternatives to drug use in food animals in addition to more research on new or novel antibiotics. It should be noted that while the NRC recognised that agricultural uses of antibiotics pose a risk to the public health, they also stated that "it does not appear to constitute an immediate public health concern." Finally, the GAO report issued April 1999 entitled, "Food Safety – The agricultural use of antibiotics and its implications for human health," recommended that "...the Secretaries of Agriculture and of Health and Human Services develop and implement a plan that contains specific goals, time frames, and resources needed to evaluate the risks and benefits of the existing and future use of antibiotics in agriculture, including identifying and filling critical data gaps and research needs."

CSPI uses the example of virginiamycin fed to turkeys with the subsequent finding of streptogramin resistant enterococci as indicative of future human clinical failures with Synercid®. It must be emphasized that enterococci do not cause disease in normal, healthy people or animals. The mere ingestion of antibiotic resistant enterococci poses no immediate hazard. Since streptogramins and macrolides have been used in the U.S. for decades, one might presume that the potential to detect human isolates with streptogramin resistance would be high if indeed the animal to human transfer occurred at a substantial rate. In fact, in a recent survey, Jones et al. (1998) reported that only 1 of 519 VRE were resistant to Synercid® (this strain was one dilution above the breakpoint) with an overall G+ susceptibility of >90% for 28,000 isolates. Moreover, virginiamycin has been used in France concurrent with the use of streptogramins in human medicine with no observed compromise.

The use of antimicrobials for the prevention of disease, whether in individual animals or a population, simply constitutes early therapeutic administration of these products. A detailed 1997 review reinforced the need for and benefits of prophylactic treatment of herds or flocks with antibiotics (Gustafson, 1997). Denial of availability of medication for the prevention of disease in animals who are at risk of disease is unethical. Allowing animals to develop frank clinical signs of disease before treatment is administered will result in unnecessary animal suffering, morbidity and mortality. Moreover, high therapeutic doses of antibiotics would be required to treat the flock or herd thereby resulting in greater antibiotic usage, potentially with the newer agents.

The elimination of subtherapeutic uses of antibiotics in feed would eliminate a significant portion of the veterinary and producer medication options. A paper by Dewey, et al cites consequences of the removal of in feed medication as increasing morbidity and mortality rates, increasing the cost of pork production, and decreased feed efficiency (Dewey, 1999). This would also trigger a need for more cropland for feed production, more animals, additional animal manure, more water usage, more therapeutic antibiotic use, and additional dead animal disposal

(Lawrence, 1998; Schwarz, 1998). A practical example is Sweden, which banned subtherapeutic uses of antibiotics in 1986 and consequently experienced an increase in total antibiotic use along with heavy-metal non-antibiotic medicaments, and lowered productivity and efficiency (Viaene, 1997; Mudd, 1998).

In conclusion, there is no scientific, medical, or regulatory basis upon which the CSPI petition should be implemented. AHI representatives would be pleased to discuss these comments further with the Center.

Sincerely,

Alexander S. Mathews

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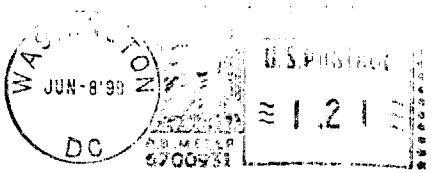

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